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Impact of meteorological factors on mumps and potential effect modifiers: An analysis of 10 cities in Guangxi, Southern China

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A R T I C L E I N F O

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A B S T R A C T

Background: In the current context of global climate change, understanding the impact of climate on respiratory infectious diseases such as mumps and the potential modified factors is crucial, especially in developing countries. However, research on the climate-related incidence of mumps is rare, inconsistent and mainly limited to a single city or region.

Methods: Daily mumps cases and meteorological variables of 10 cities in Guangxi, Southern China were collected for 2005–2017. Two-stage analyses were performed to assess the relationship between meteorological factors and mumps incidence during two time-periods: 2005–2012 and 2013–2017, separately. First, a Poisson regression model that allows over-dispersion was used to estimate the city-specific climate-related morbidity after controlling for temporal trends, day of week, and national statutory holidays. Then, we used a multivariate meta-analytical model to pool the city-specific effect estimates and conducted subgroup analyses. Multivariate meta-regression was applied to detect potential effect modifiers.

Results: Non-linear relationships were observed among mean temperature, wind speed, and mumps incidence in 2005–2012. The impact of high temperature on mumps incidence was short and rapid, whereas the impact of low temperature was long and slow. The total cumulative relative risk (RR) associated with hot temperature was 1.18 [95% Confidence Interval (CI): 0.93, 1.48], which was calculated by comparing the incidence of mumps above the 90th percentile of temperature with its incidence at the median temperature at lag of 0–30 days. Meanwhile, the RR associated with cold temperature was calculated to be 1.50 (95% CI: 1.08, 2.10) by comparing the incidence of mumps below the 10th percentile of temperature with its incidence at the median temperature. Similarly, the RRs associated with windless and windy conditions for the total population were 1.23 (95% CI: 1.04, 1.46) and 0.83 (95% CI: 0.67, 1.02), respectively. Effects based on extreme temperature and wind speed conditions were more prominent in males than in females. Compared with children and adults, adolescents (5–14 years old) were more sensitive to extreme weather conditions. Geographical latitude, Population density, GDP per capita, Number of health institutions, Highly educated population and Inoculation rate were considered the most likely associated modifiers. In addition, the correlation between meteorological factors and the incidence of mumps and modification of socioeconomic factors after 2013 showed similar curves compared with results in 2005–2012, but the cumulative effect was not statistically significant.

Conclusions: Meteorological factors, such as temperature and wind speed, exert a significant impact on the incidence of mumps. The relationship varies depending on gender and age. Socioeconomic factors such as vaccination, GDP, geographical latitude, etc. may substantially affect the weather-related mumps incidence.

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1. Introduction

Mumps is an acute respiratory infection caused by a virus of the paramyxovirus family and is characterized by unilateral or bilateral swollen and painful parotid gland, accompanied by fever, headache, nausea, and vomiting (Hviid et al., 2008). Although the symptoms of the disease are mild and the mortality rate is low, the disease can cause a series of serious complications, such as meningitis, oophoritis, and neurological deafness (Yung et al., 2011). Direct contact is the main route for mumps transmission, and the average incubation period of the disease is 19 days (12–25 days) (Cui et al., 2014). The incidence of mumps has been under control since the introduction of a mumps vaccine in the expanded program on immunization (EPI) in 2008, and children between the ages of 18 and 24 months can receive a free dose of the measles–mumps–rubella vaccine; however, outbreaks on cyclical mumps have frequently occurred in the past 10 years, and this phenomenon has also been observed in many other countries worldwide (Barskey et al., 2009; Cui et al., 2014; Fpl, 2008; Sane et al., 2014; Vandermeulen et al., 2009). China, as the most populous country in the world, always have a higher incidence of mumps compared with other countries. The number of reported mumps cases in China was estimated to rank the highest worldwide in 2016 (accounting for approximately 30.01% of the total) (WHO, 2016). Meanwhile, children in most parts of China are only vaccinated with one dose of mumps vaccine, while studies suggested that three doses of mumps vaccination can enable people to obtain stable immunity (Marin et al., 2018; Webber et al., 2017). This suggests that the mumps epidemic may continue to outbreak as the continuous attenuation of the body's antibody level and the accumulation of susceptible population. As a result, mumps prevention and control has become one of the main public health issues that the Chinese government must confront. The incidence of mumps shows a clear seasonal pattern in China, with most cases occurring between April and July, with another small peak in November and December (Cui et al., 2014). However, the seasonal pattern between the northern and southern parts of China differ, showing a double-peak distribution (May–June and December–January) in Jinan but a single-peak distribution (May–June) in Guangzhou (Li et al., 2017; Yang et al., 2014). This observation suggests that the incidence of mumps is influenced by climatic conditions in different regions.

Weather plays an important role in death (Guo et al., 2016), preterm delivery (Basu et al., 2017), waterborne diseases (Herrador et al., 2015) and vector-borne diseases (Zhang et al., 2016). However, few studies have investigated the impact of meteorological factors on respiratory infectious diseases, especially mumps, despite the existence of published reports demonstrating that climatic factors can promote viral infections through different mechanisms, such as increasing viral survival, influencing viral climate-dependent life cycle processes, or modulating the pediatric population's immune response (Nenna et al., 2017; Paynter et al., 2015; Tang and Loh, 2014). However, experiments with animal models and clinical studies do not always support this simple interpretation. A study conducted in Taiwan showed that the number of mumps cases increases at 20 °C and then declines at temperatures higher than about 25 °C, producing an inverted V-shaped curve (Ho et al., 2015). Another study performed in Jining, China found that meteorological factors exert a threshold effect on the incidence of mumps, showing an approximately linear correlation when the meteorological variables exceed a certain value (Li et al., 2016). A Japanese study found that temperature and humidity could increase the risk of mumps, and the risk tended to increase with age; this result is consistent with the results obtained in Guangzhou, China (Onozuka and Hashizume, 2011; Yang et al., 2014). Hu et al. found that the incidence of mumps was related to all the included meteorological factors in a study of four cities in Fujian, while they did not combine the results of the four cities (Hu et al., 2018). Previous studies on the relationship between meteorological factors and mumps incidence were mainly based on a single city or a region such as Taiwan (China). Multi-city studies on this topic have yet to be conducted. Those studies also usually followed different study designs and model specifications, which limit the ability to compare results across cities. In addition, the research results are unstable largely because of the poorly understood heterogeneity across cities due to differences in climate, socioeconomic factors, and behavioral lifestyles. Thus, further evidence is needed to assess the health impacts of different weather indicators from large geographical areas and determine possible sources of heterogeneity.

In this study, 10 cities in Guangxi, Southern China were included to estimate the effects of meteorological factors on the incidence of mumps on the basis of a two-stage analysis. These cities not only suffer from severe epidemics but also show uneven economic development. Since they are located in the subtropical monsoon region, they are susceptible to experiencing extreme weather conditions. Meanwhile, few studies have explored the relationship between the incidence of mumps and meteorological factors after 2013 in China. Previous studies on the climate-related mumps incidence conducted in Guangzhou, Jining and Fujian limited the time period to 2005–2012, 2009–2013 and 2005–2013, respectively. However, the epidemic trend of mumps after 2013 is quite different from the past, which suggests the urgency of the study for this time period. Therefore, we analyzed the data of the two periods: 2005–2012 and 2013–2017, simultaneously.

Our objective was to define the overall cumulative exposure response and the lag response and explore the potential sources of heterogeneity. This study could provide useful information to formulate effective intervention policies for the prevention and control of infectious diseases.

2. Materials and methods

2.1. Study area

The Guangxi Zhuang Autonomous Region, located in the southwestern part of China, is the only coastal autonomous prefecture, and it is inhabited by many different ethnic groups (geographical coordinates: 20°54'–26°24' N, 104°26'–112°04' E, Fig. 1a). It covers a land area of 236,700 km^2, and its total population was 47.96 million in 2015. A total of 14 cities are under the jurisdiction of Guangxi, and 10 of these were selected as research areas for this study, considering data availability. Guangxi is located in a typical subtropical monsoon climate zone. Most parts of the region have a warm climate with abundant heat and rainfall, clear wet and dry periods, and no apparent seasonal changes. The winter is short, dry, and warm, whereas the summer is long, wet, and hot.

2.2. Data collection

Daily data on the incidence of mumps between 2005 and 2017 were obtained from the Infectious Disease Reporting System of the Guangxi Center for Disease Prevention and Control. The system was utilized in 2004 and includes an established network between local medical institutions through modern means of communication. It forms part of an information networking system for disease prevention and control, connecting institutions at the national, provincial, municipal, and county levels. The information network also extends to towns and urban communities, and forms a unified, efficient, fast, and accurate reporting system for infectious disease epidemics. The increasing internet big data integration and cloud storage capabilities can provide certain guarantees for this real-time reporting system (Hossain et al., 2017; Memos et al., 2017). A total of 39 infectious diseases are currently included in the reporting system, and mumps is listed as a Category C infectious disease in China. Health departments require that infected patients and patients with suspected infection or infectious pathogen carriers classified under this category must be reported online within 24 h once diagnosed or be reported by means of a network report card filled out by trained health personnel and sent within 24 h if the

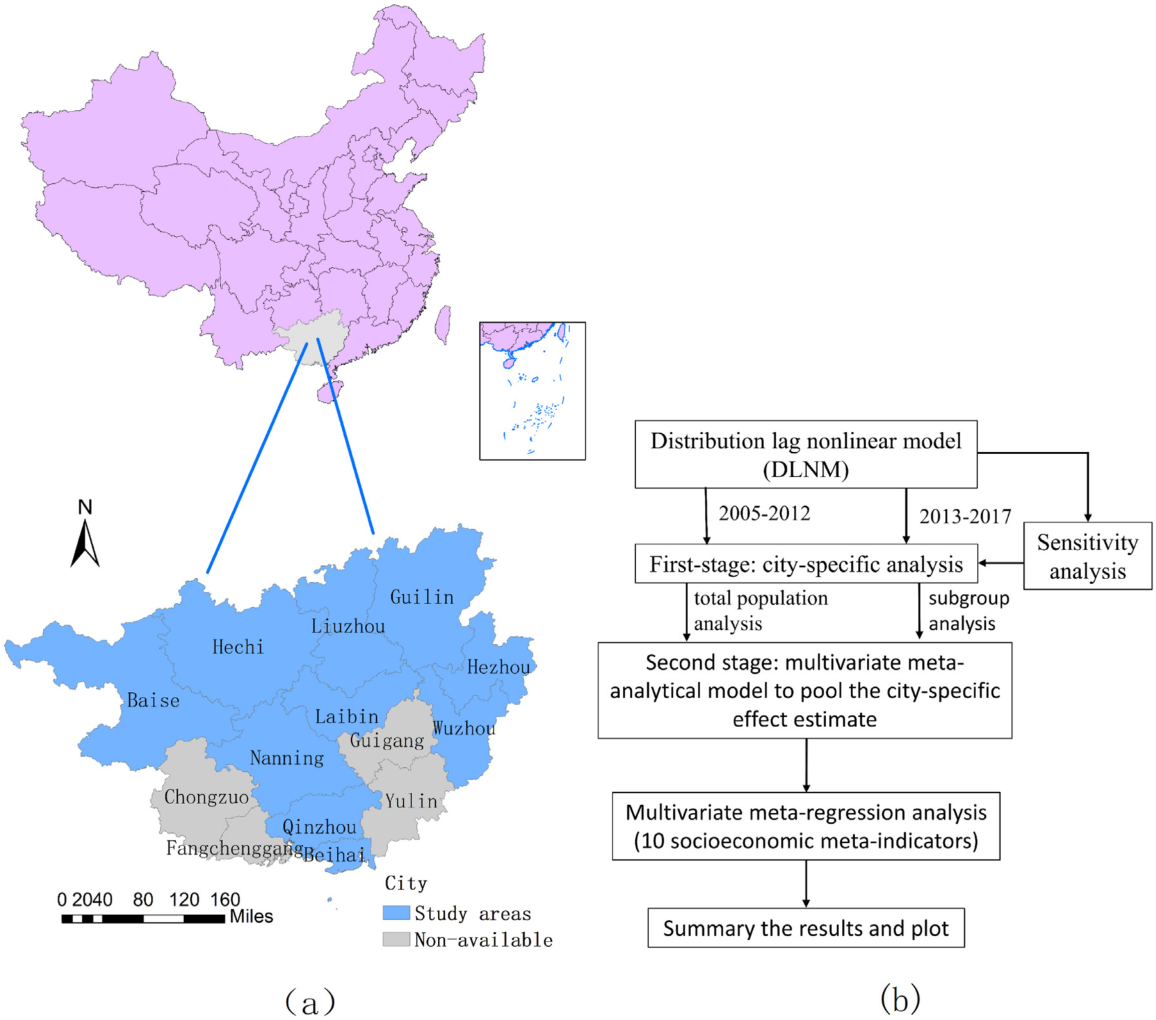

Fig. 1. (a) Geographical location of 10 cities of Guangxi in China, 2005–2017; (b) A brief summary of the methods used in this study.

medical institution does not have Internet access. All disease-reporting data are reviewed by professionals to ensure their accuracy and reliability. The diagnosis of mumps cases was based on the "Diagnostic Criteria for Mumps" issued by the Ministry of Health; these criteria did not change significantly during the study period (China, 2007).

City-specific daily meteorological data for the same time period were downloaded from the publicly accessible China National Weather Data Sharing System (http://data.cma.cn/site/index.html). The datasets were collected by the meteorological departments of each province and reported to the National Meteorological Center. Meteorological data include daily minimum temperature, average temperature, maximum temperature, atmospheric pressure, relative humidity, sunshine duration, and wind speed. The socioeconomic and demographic information involved in this study was mainly collected from the Guangxi Statistical Yearbook (2005–2016), the 2010 population census of Guangxi Zhuang Autonomous Region and the 2015 1% population sample survey of Guangxi Zhuang Autonomous Region. Vaccination data were obtained from the Guangxi Center for Disease Control and Prevention.

2.3. Data analysis

This study included data from 10 cities in Guangxi for analysis. Time series analysis and Spearman rank correlation tests were conducted to describe the basic pattern of data distribution, as well as the linear relationship between the number of cases and meteorological variables and between different meteorological variables. Our initial analysis suggested that the incidence of mumps showed no remarkable linear relationship to any of the meteorological indicators (Fig. S1). To control the confounding effect of other meteorological variables, especially mean temperature and relative humidity, we included all the studied meteorological variables, except for atmospheric pressure, into the model to explore their extreme and lag effects on the incidence of mumps. In addition, previous study also found that the seasonality of the mumps incidence became remarkably weaker after 2013, and the overall vaccination situation of the vaccine was also different from before. In order to control the potential cofounding effect of vaccination, we conducted modeling analysis on the data for 2005–2012 and 2013–2017 separately to evaluate the possible changes. We utilized a two-stage statistical approach to estimate climate-related morbidity risk at the provincial level (Fig. 1b). In the first stage, we applied a time series model to derive estimates of city-specific climate–morbidity relationship. These estimated relationships were then pooled in the second stage at the province level using meta-analysis. This approach has been described in previous publications (Antonio and Ben, 2013; Gasparrini et al., 2013). Sensitivity analysis of the selected model was also conducted to ensure its optimization.

2.3.1. First-stage time series model

Basing on the data distribution and the relationship between variables, we selected a quasi-Poisson regression model combined with the Distributed Lag Nonlinear Model (DLNM) to estimate the city-specific

Table 1
Description of meteorological factors and mumps cases in 10 cities of Guangxi, 2005–2017.

Variable	Minimum	P10	P25	P50	P75	P90	Maximum	Mean ± SD
Mean temperature	− 0.7	11	16	23.4	27.4	29.4	33.5	21.6 ± 7.0
Relative humidity	20	59	68	77	84	90	100	75.5 ± 12.2
Wind velocity	0.0	0.9	1.2	1.6	2.2	3.0	8.6	1.8 ± 0.9
Sunshine duration	0.0	0.0	0.0	3.7	7.9	9.6	12.8	4.2 ± 3.9
Atmospheric pressure	966.0	985.1	991.6	999.1	1006.6	1013.1	1034.5	999.0 ± 10.8
Case	0	0	1	2	5	9	50	3.9 ± 4.7

SD: standard deviation; Px: percentile of the data.

effect of meteorological conditions on the incidence of mumps. Four meteorological variables such as mean temperature, wind speed, relative humidity and sunshine duration (atmospheric pressure was excluded due to collinearity) were included in the model. The Poisson regression model allowing for over-dispersion for each city was expressed as follows:

$$\mathrm{Y}_t \sim Poisson(u) = \alpha + NS(M, df, lag, df) + \sum NS \quad (X_i) + NS(Time, df) + \beta DOW_t + \gamma Holiday_t$$

where t is the day of observation; Y_t is the observed incidence cases of mumps on t; α is the intercept; NS is a natural cubic spline that was used to model the nonlinear relationship between meteorological variables and the incidence of mumps; M is the examined meteorological variable that is closely related to the incidence of mumps; X_i refers to several other meteorological variables that should be controlled due to their modifying effect on the incidence of mumps, M and X_i were all the matrixes obtained by applying cross-basis functions to each of them; *Time* is the indicator variable to control for long-term trend, seasonality; *DOW* is the day of week; and *Holiday* refers to a covariate to control the effect of public holidays. In this model, the degrees of freedom (*df*) per year for time variable was set to 6. We also defined natural cubic spline bases as 3, 3, 5, 3 *df* for mean temperature, relative humidity, wind speed and sunshine duration, respectively. Accordingly, the *df* values of lag spaces were set at 3, 4, 4 and 3, and the maximum lag days were set at 30, 24, 24 and 24, respectively. The *df* was determined based on the Akaike information criterion for quasi-Poisson (Q-AIC) and the residual autocorrelation, which can produce the optimal model. In addition, the selection of the maximum lag days was based on the incubation period for mumps and on previous studies (Yang et al., 2014). All knots were placed by default at equally spaced values in the space of each meteorological variable, and the knots for the spline for lags were also placed at equally spaced values on the log scale of lags.

Considering that the median value of meteorological variables is the most frequently exposed meteorological condition in the daily life of people, we set it as a reference point to examine the extreme effects of meteorological variables and compared them with data included above the 90th or below the 10th percentile to calculate the relative risk (RR). Extreme effects are defined as follows: hot effect and cold effect, dry effect and wet effect, windy effect and windless effect, and sunny effect and cloudy effect. The variation ranges of the meteorological variables in each city are basically the same because of the small study area and the similar meteorological conditions. Hence, we selected a uniform threshold for all cities to establish the model. In addition, stratified analysis was performed by gender and three age-groups (i.e., children 0–4 years old, adolescents 5–14 years old and adults 15- years old), which can help us identify vulnerable populations to climate-related mumps incidence.

2.3.2. Second stage meta-analysis

In the second stage, we used a multivariate meta-analysis to pool the city-specific effect estimates obtained from the first stage model. The random-effect meta-analysis was fitted by maximum likelihood estimation to examine both within and between city variations regarding effect estimates. Ten indicators, including geographic location, economy, population, health care, and education, were included in this study to explore possible modifiers of climate-induced morbidity. The modified effects of socioeconomic factors can be identified by a multivariate Wald test. Heterogeneity among cities was assessed by the I^2 statistic and Cochran Q test, which quantifies the percentage of variability due to true differences across cities (Higgins and Thompson, 2002). The application of multivariate meta-analysis and meta-regression to synthesize estimates of multi-parameter associations can be found in previous studies (Gasparrini and Armstrong, 2011; Gasparrini et al., 2012).

Sensitivity analyses were also performed on city-specific models to test the robustness of the results. We changed the *df* for seasonality and long-term trend (2–18 *df*), meteorological variables (2–11 *df*), and for lag space (2–14 *df*). Following a previous study (Yang et al., 2014), we selected the optimal DLNM type (natural cubic spline, combined with survival analysis, or combined with Poisson regression for case-crossover design) and temperature measurement based on Q-AIC values. The results of the sensitivity analysis are provided in the Supplementary Materials section (Table S1–S5).

We used R software (version 3.2.2, R Development Core Team 2017) to conduct data analysis. City-specific exposure-response relationships were estimated using R package “dlnm.” Multivariate meta-analysis was conducted using package “mvmeta.” This study was approved by the Guangxi Medical University Ethics Committee. All data included in the analysis were anonymized.

3. Results

Table 1 summarized the information on meteorological factors and the incidence of mumps. A total of 183,341 mumps cases were reported in 10 cities of Guangxi between 2005 and 2017. The daily average number of mumps cases was 4 (range: 0–50) for the study area. The daily mean temperature for the 10 cities was 21.6 °C (range: -0.7–33.5 °C), with Guilin showing the lowest (−0.7 °C) and Liuzhou the highest (33.5 °C). The daily mean relative humidity, mean wind velocity, mean sunshine duration, and mean atmospheric pressure were 75.5% (range: 20–100%), 1.8 m/s (range: 0–8.6 m/s), 4.2 h (range: 0–12.8 h), and 999.0 hPa (range: 966 hPa to 1034.5 hPa), respectively. The time-series analysis of mumps cases and meteorological factors indicated that the incidence of mumps showed a cyclical and long-term trend. Two substantial peaks were observed during the study period: the first peak lasted from April to July, and the second peak lasted from October to January of the following year. Overall, the incidence of mumps gradually decreased, and the seasonal mumps trend was not as clear after 2013. The mean temperature, relative humidity, sunshine duration, and atmospheric pressure also showed remarkable seasonal fluctuations, and their trends were relatively stable (Fig. 2.).

Fig. 3 and Fig. S2 showed the cumulative effect of the maximum lag day at different levels of each meteorological factor in 2005–2012 and 2013–2017, respectively. Results indicated that the cumulative effects of different mean temperature on the mumps incidence showed a curve pattern of rising first, then declining and rising again. This trend was basically the same across different population subgroups, except for the

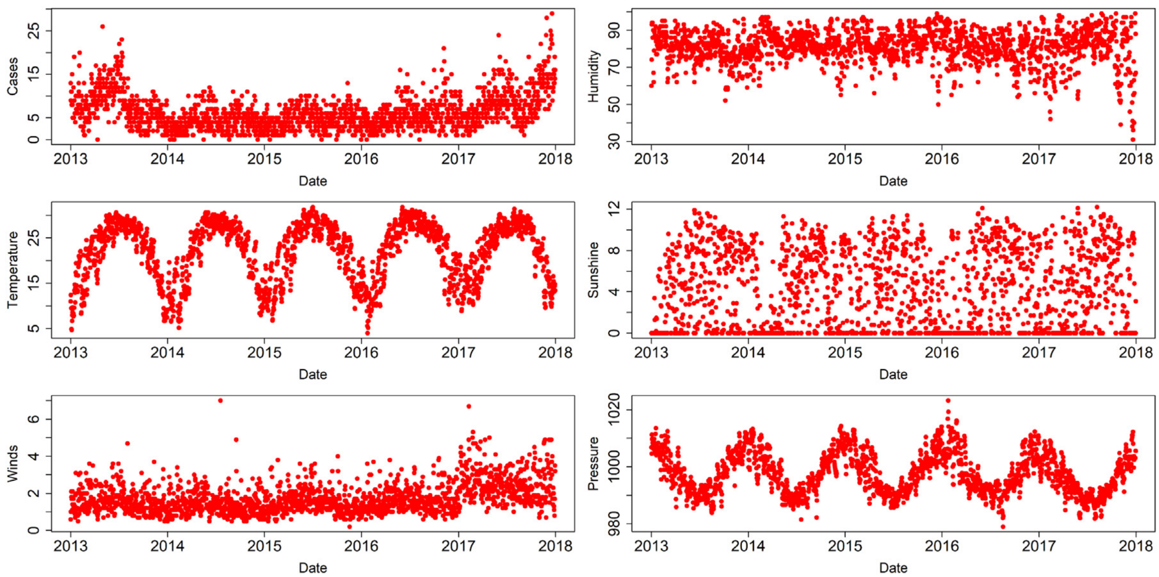

Fig. 2. Time-series results between meteorological factors and mumps incidence in Guangxi, 2005–2017.

adult group who showed a curve pattern of rising first and declining later in 2005–2012. The maximum RR corresponded to the mean temperature of approximately 12–13 °C. Nevertheless, the effects of temperature on different subgroups were not exactly the same. Low temperatures exerted a great impact on adolescents (5–14 years old) and males, whereas high temperatures demonstrated a great impact on adolescents (5–14 years old). Results also showed that wind speed could influence the incidence of mumps. A low wind speed could increase the incidence of mumps, whereas effects of high wind speed were not obvious. Male group and adults (15– years old) were more sensitive to wind speed. In 2013–2017, although the effects of mean temperature and wind speed on the mumps incidence showed a similar curve trend, effects in each of the groups were not significant (Fig. S2). Relative humidity and sunshine duration exhibited no substantial effects on the incidence of mumps both in 2005–2012 and in 2013–2017.

Extreme effect analysis showed that the incidence of mumps and mean temperatures were closely related in 2005–2012. Hot average temperatures exerted an acute, short-term effect, whereas cold temperatures demonstrated a chronic, long-lasting effect on the incidence of mumps (Fig. 4). The hot temperature effect generally occurred within

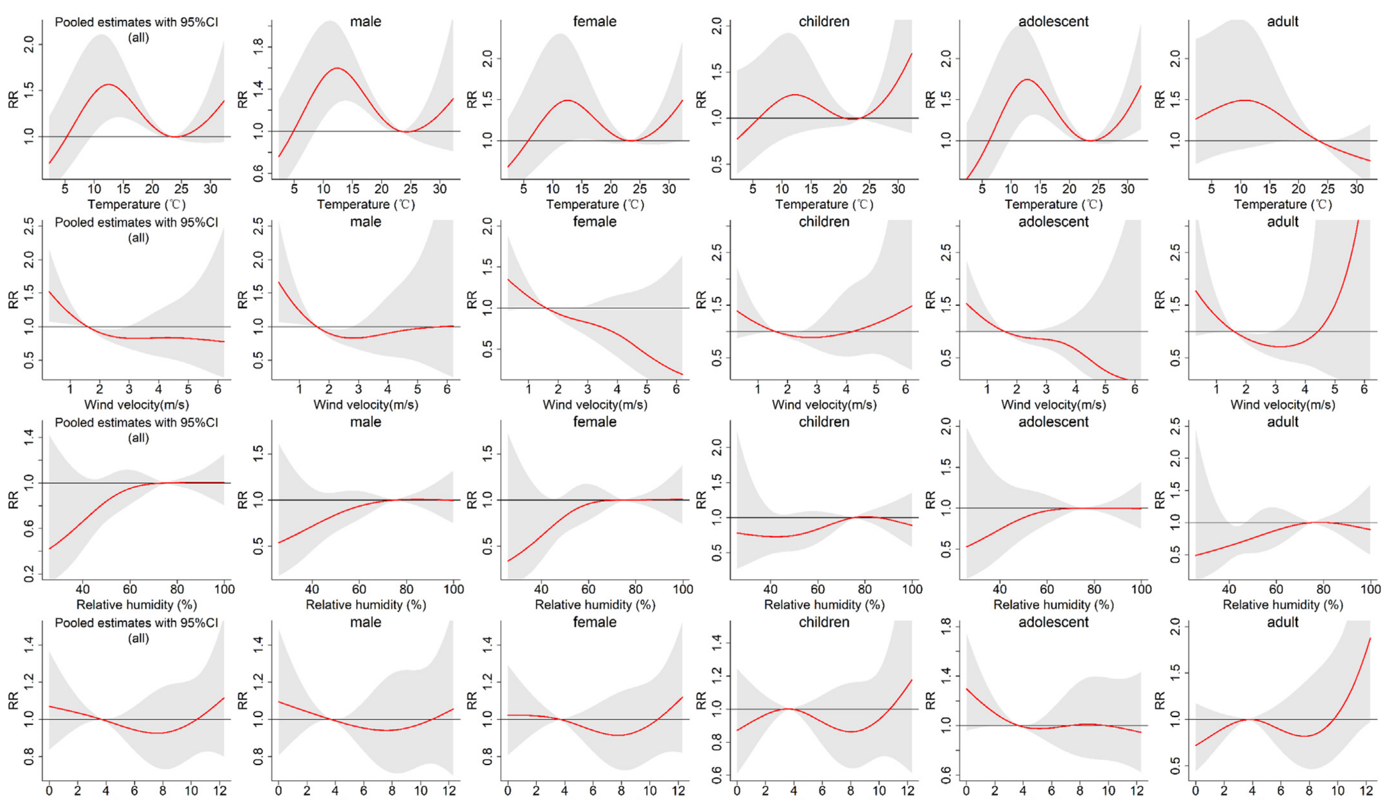

Fig. 3. Overall cumulative summary associations between the incidence of mumps and meteorological factors for all groups in 2005–2012. The children, adolescents, and adults in the figure correspond to ages 0–4, 5–14, and 15–years, respectively.

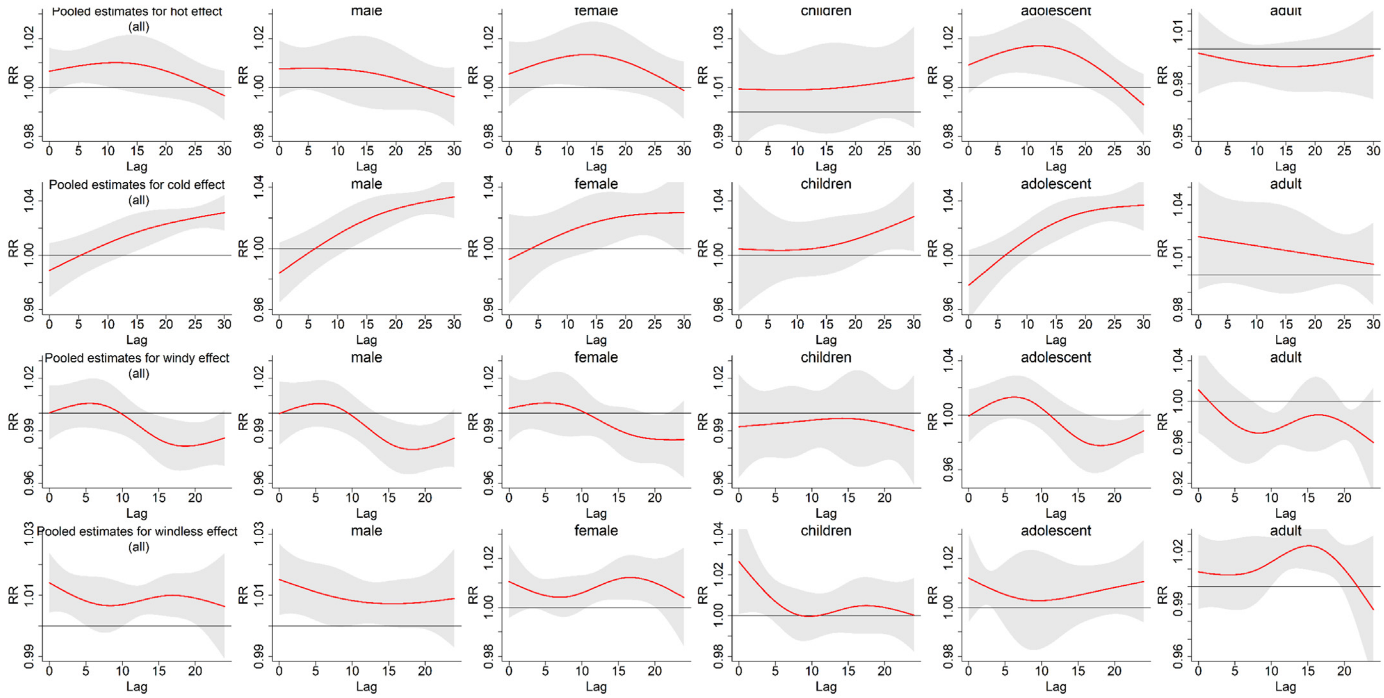

Fig. 4. Overall cumulative summary associations between the incidence of mumps and extreme weather conditions of mean temperature (hot effect, cold effect) and wind velocity (windy effect, windless effect) for all groups at different lag days in 2005–2012. The hot and windy effects were estimated by the relative risk (RR) of mumps with comparison to the 90th percentile of daily mean temperature and daily wind velocity to their median, respectively. The cold and windless effects were estimated by the RR of mumps with comparison to the 10th percentile of daily mean temperature and daily wind velocity to their median, respectively.

Table 2
Extreme effect analysis of different meteorological factors in 2005–2012. The Relative Risk (RR) was used to estimate the effect in different subgroups. Notably, age for children, adolescents, and adults in this study are defined as 0–4, 5–14, and 15 years, respectively.

	RR (95% CI) estimate for subgroups					
effect variables	all	male	female	children	adolescent	adult
hot effect	1.18(0.93,1.48)	1.14(0.85,1.52)	1.23(0.97,1.58)	1.36(0.89,2.07)	1.30(1.03,1.65)	0.82(0.62,1.09)
cold effect	1.50(1.08,2.10)	1.54(1.17,2.04)	1.43(0.89,2.29)	1.23(0.79,1.92)	1.62(1.10,2.38)	1.49(0.90,2.47)
windy effect	0.83(0.67,1.02)	0.83(0.66,1.05)	0.82(0.65,1.04)	0.89(0.66,1.20)	0.85(0.68,1.06)	0.72(0.50,1.03)
windless effect	1.23(1.04,1.46)	1.29(1.04,1.59)	1.17(0.99,1.37)	1.18(0.95,1.46)	1.24(1.00,1.52)	1.34(0.98,1.83)
wet effect	1.01(0.92,1.10)	1.01(0.89,1.14)	1.01(0.89,1.14)	0.98(0.81,1.19)	1.00(0.89,1.12)	0.97(0.76,1.23)
dry effect	0.94(0.79,1.12)	0.92(0.77,1.10)	0.94(0.76,1.17)	0.82(0.61,1.09)	0.96(0.78,1.18)	0.86(0.59,1.24)
sunny effect	0.97(0.78,1.20)	0.97(0.74,1.27)	0.95(0.76,1.19)	0.91(0.70,1.19)	1.00(0.72,1.39)	0.98(0.56,1.72)
cloudy effect	1.07(0.84,1.37)	1.10(0.81,1.49)	1.02(0.81,1.29)	0.87(0.61,1.25)	1.30(0.96,1.75)	0.72(0.44,1.17)

0–18 days after exposure. Adolescents was the most sensitive group than other subgroups, and the cumulative effect at 30 lag days was RR (CI 95%): 1.30 (1.03, 1.65) (Table 2). The cold temperature effect generally occurred on day 11–12 after exposure. Males and adolescents (5–14 years old) were highly sensitive, and the cumulative effects at 30 lag days were RR (CI 95%): 1.54(1.17, 2.04) and 1.62(1.10, 2.38), respectively. Wind velocity was another meteorological variable that could affect the incidence of mumps in 2005–2012. Windless conditions could produce substantial adverse effects on the total population. The RR for the total population increased to 1.23(1.04, 1.46). Windless effects were more prominent in the male and adolescent population, with RR (CI 95%): 1.29(1.04, 1.59) and 1.24(1.00, 1.52), respectively. Adults also had a certain sensitivity to windless effect, but the specific cumulative effect value were not significant. Compared to results in 2005–2012, the impact of extreme weather on the incidence of mumps was significantly reduced after 2013, and the group of susceptible people also substantially decreased. Lag effects were also observed in the relationship between extreme temperature and mumps incidence (Fig. 5). Hot effect showed rapid hysteresis on groups of males, children and the adolescents, while only the adolescents were markedly affected by cold effect, and the lag effect appeared later. The cumulative effects of extreme temperature on the mumps incidence at 30 lag days were not as obvious as which in 2005–2012. Only males for hot effect was found to be statistically significant, with RR (CI 95%): 1.35(1.04, 1.75) (Table S6). No effects of wind velocity on different population subgroups had been observed. Similarly, meteorological factors like relative humidity and sunshine duration did not show cumulative effects and lag effects on the mumps incidence both in 2005–2012 and 2013–2017 (Fig. S3-S4).

The results of the heterogeneity analysis for all included meteorological variables between 2005 and 2017 are shown in Table 3 and Table S7, with a comparison of statistics from the random-effect meta-analyses (no meta-predictor) and random-effect meta-regression with a single meta-predictor (socioeconomic indicator). Results of the Cochran Q tests and I^2 suggest a strong heterogeneity in the effect estimate of different meteorological variables, with a highly significant Wald test (P-value < 0.05) and $I^2 > 50\%$. Results of the heterogeneity test from 2005 to 2012 suggested that there exist certain heterogeneities in the impact of meteorological variables on mumps incidence. Latitude was the most contributing factor to the heterogeneity of temperature-

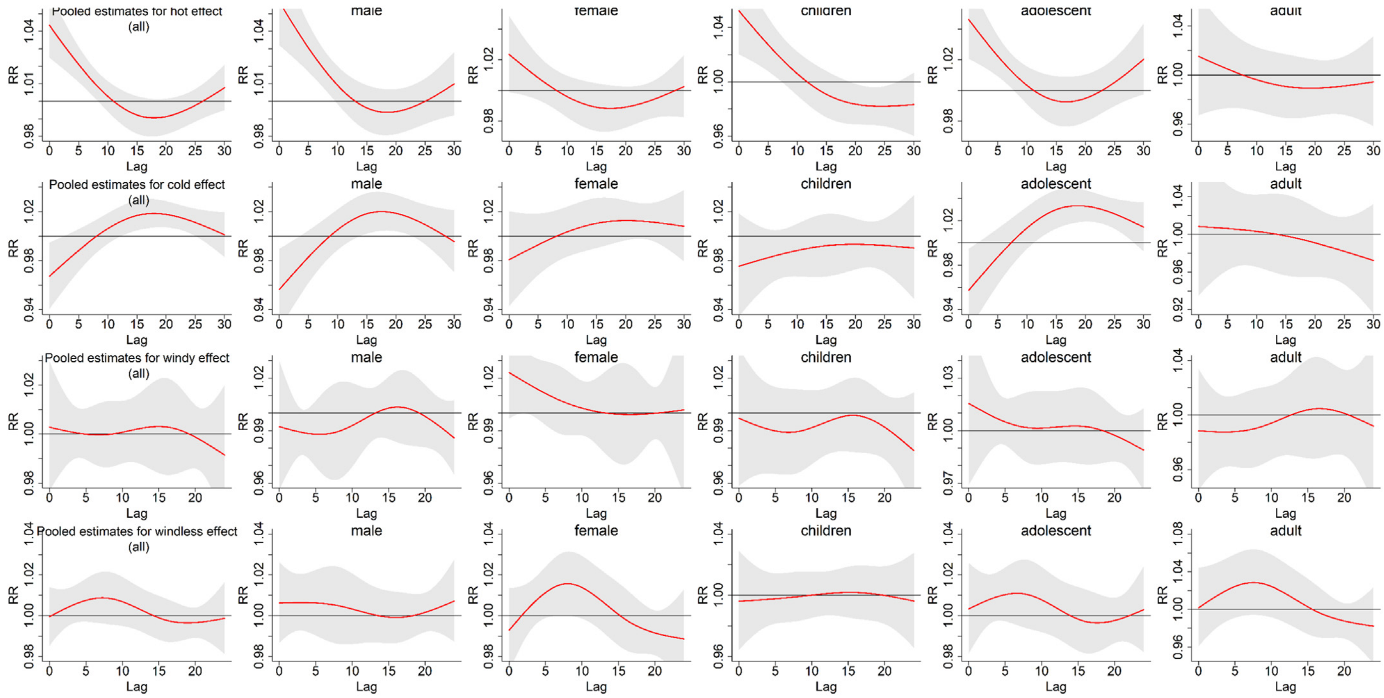

Fig. 5. Overall cumulative summary associations between the incidence of mumps and extreme weather conditions of mean temperature (hot effect, cold effect) and wind velocity (windy effect, windless effect) for all groups at different lag days in 2013–2017. The hot and windy effects were estimated by the relative risk (RR) of mumps with comparison to the 90th percentile of daily mean temperature and daily wind velocity to their median, respectively. The cold and windless effects were estimated by the RR of mumps with comparison to the 10th percentile of daily mean temperature and daily wind velocity to their median, respectively.

related morbidity, with the Wald test value < 0.001 and the I^2 value decreasing remarkably: from 72.9 to 57.3. The population density also contributed more to the heterogeneity of the effect of wind speed related mumps incidence. The corresponding Wald test result was 0.027. The I^2 value had a certain degree of decline when the indicator was included in Multivariate meta-regression analysis as a meta-predictor (from 65.6 to 63.9). Results of heterogeneity analysis in 2013–2017 indicated that the heterogeneity degree of the climatic-related morbidity is significantly reduced. Almost all the meteorological variables had an I^2 value < 50. No socioeconomic factor was found to have a significant contribution to the heterogeneity of climate-related incidence. Considering the considerable effect of temperature on human health and the adaptability of human to temperature change, we further described the effects of socioeconomic factors on the incidence of mumps at different temperature conditions. We found that higher latitude can increase the risk of mumps both people are in an extremely cold and hot environment in 2005–2012, with RR values: 1.95(1.35,2.83) and 1.44(1.12,1.86), respectively (Fig. 6 and Table 4). Rural population had a similarly curved trend, but its cumulative effect was not statistically significant. In extremely low temperature

Table 3
Modification effects of socioeconomic factors on weather-related morbidity of mumps in 2005–2012: multivariate Wald test on the significance of each meta-predictor in explaining variation in overall population temperature–disease curves, Cochran Q test for heterogeneity, I^2 statistics for residual heterogeneity.

Predictor	Heterogeneity test	Mean temperature	Wind velocity	Relative humidity	Sunshine duration
no meta-predictor	I^2(p-value)	72.9(< 0.001)	65.6(< 0.001)	69.6(< 0.001)	63.0(< 0.001)
Latitude (degree North)	Wald test	< 0.001	0.341	0.409	0.227
	I^2(p-value)	57.3(< 0.001)	65.9(< 0.001)	69.4(< 0.001)	64.1(< 0.001)
population density (persons per sq.km)	Wald test	0.317	0.027	0.368	0.516
	I^2(p-value)	72.4(< 0.001)	63.9(< 0.001)	69.8(< 0.001)	63.7(< 0.001)
GDP per capita (RMB)	Wald test	0.423	0.536	0.423	0.641
	I^2(p-value)	75.3(< 0.001)	66.9(< 0.001)	68.5(< 0.001)	66.3(< 0.001)
Children population (%)	Wald test	0.059	0.901	0.569	0.764
	I^2(p-value)	73.9(< 0.001)	67.7(< 0.001)	71.2(< 0.001)	65.4(< 0.001)
Number of children (per primary school)	Wald test	0.291	0.089	0.992	0.981
	I^2(p-value)	73.0(< 0.001)	64.8(< 0.001)	72.6(< 0.001)	67.1(< 0.001)
Numbers of health institutions (per 10,000)	Wald test	0.100	0.491	0.085	0.545
	I^2(p-value)	73.0(< 0.001)	65.7(< 0.001)	67.4(< 0.001)	62.4(< 0.001)
Numbers of beds in health institutions (per 1000)	Wald test	0.753	0.881	0.449	0.473
	I^2(p-value)	75.5(< 0.001)	68.6(< 0.001)	65.4(< 0.001)	65.5(< 0.001)
Highly educated population (%)	Wald test	0.870	0.889	0.267	0.101
	I^2(p-value)	75.4(< 0.001)	68.9(< 0.001)	65.2(< 0.001)	60.6(< 0.001)
Rural population (%)	Wald test	0.668	0.398	0.481	0.690
	I^2(p-value)	75.3(< 0.001)	66.4(< 0.001)	69.7(< 0.001)	66.0(< 0.001)
Inoculation rate (%)	Wald test	0.121	0.271	0.157	0.863
	I^2(p-value)	73.9(< 0.001)	66.8(< 0.001)	67.3(< 0.001)	64.4(< 0.001)

Note: Inoculation rate (%): the average amount of vaccine inoculated divided by the average population aged 0–4 years.

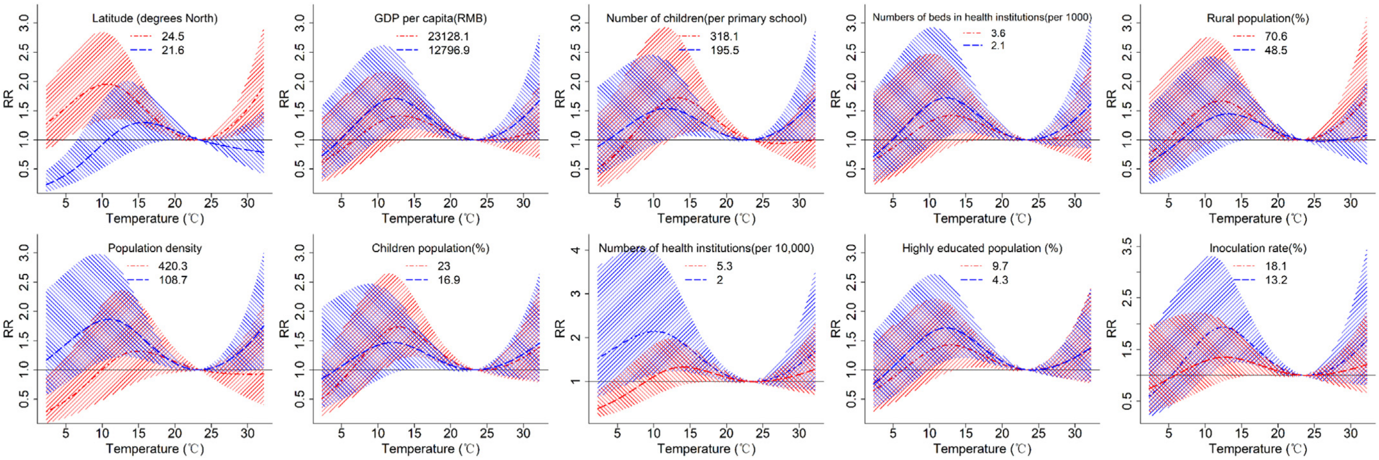

Fig. 6. Meta-regression analysis of the incidence of mumps and socioeconomic factors at different mean temperature and predictor levels in 2005–2012.

Table 4
Results of overall effects at two predictor levels of each of the socioeconomic factors under extreme temperature conditions in 2005–2012. Cpall10 refers to the predicted value of the cumulative effect under extreme temperature environment corresponding to the 10th quantile of each socioeconomic indicator value, while cpall90 corresponding to the 90th quantile of each socioeconomic indicator value.

Predictor	cpall10 for hot effect	cpall90 for hot effect	cpall10 for cold effect	cpall90 for cold effect
Latitude	0.84(0.56,1.25)	1.44(1.12,1.86)	0.98(0.55,1.73)	1.95(1.35,2.83)
Population density (persons per sq.km)	1.36(0.98,1.88)	0.93(0.56,1.55)	1.86(1.17,2.95)	1.06(0.51,2.19)
GDP per capita (RMB)	1.32(0.97,1.80)	1.06(0.77,1.47)	1.65(1.04,2.62)	1.32(0.81,2.17)
Children population (%)	1.23(0.86,1.76)	1.17(0.83,1.66)	1.44(0.86,2.43)	1.59(0.97,2.61)
Number of children (per primary school)	1.34(0.98,1.84)	0.96(0.63,1.46)	1.52(0.94,2.44)	1.56(0.84,2.89)
Numbers of health institutions (per 10,000)	1.32(0.85,2.07)	1.13(0.79,1.63)	2.14(1.19,3.87)	1.16(0.71,1.89)
Numbers of beds in health institutions (per 1000)	1.29(0.87,1.91)	1.09(0.73,1.63)	1.65(0.93,2.93	1.34(0.72,2.47)
Highly educated population (%)	1.17(0.84,1.63)	1.18(0.83,1.66)	1.66(1.05,2.63)	1.36(0.83,2.21)
Rural population (%)	1.01(0.70,1.48)	1.36(0.96,1.92)	1.35(0.75,2.43)	1.62(0.95,2.76)
Inoculation rate (%)	1.31(0.84,2.03)	1.10(0.75,1.59)	1.82(1.00,3.31)	1.30(0.77,2.19)

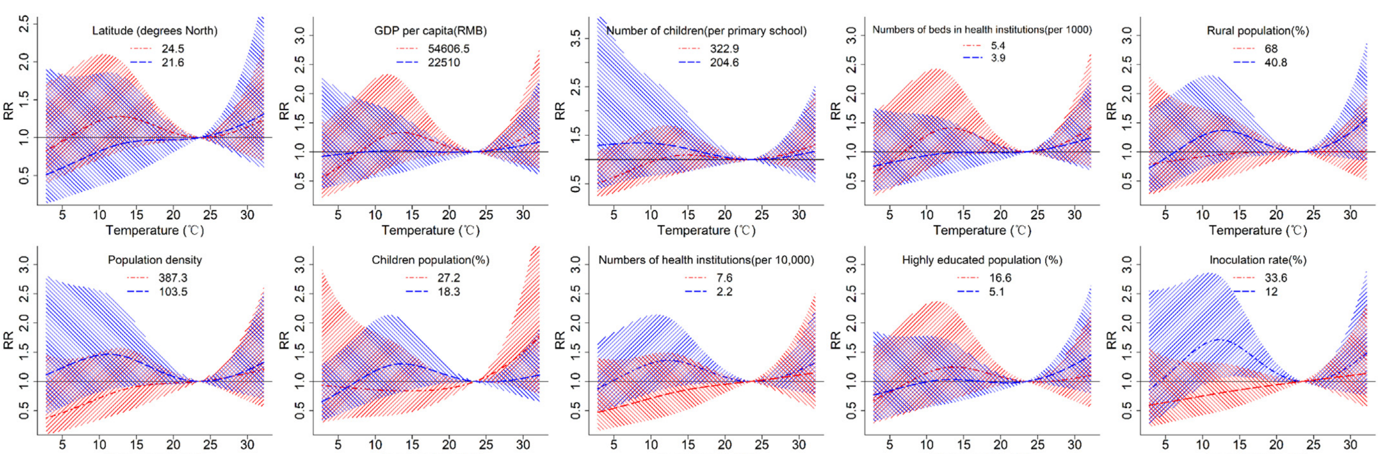

Fig. 7. Meta-regression analysis of the incidence of mumps and socioeconomic factors at different mean temperature and predictor levels in 2013–2017.

environment, lower population density, GDP per capita, numbers of health institutions, highly educated population and inoculation rate were all risk factors for the mumps incidence, with their corresponding RR values were 1.86(1.17,2.95), 1.65(1.04,2.62), 2.14(1.19,3.87), 1.66(1.05,2.63) and 1.82(1.00,3.31), respectively. Results of the modified effect analysis with respect to the climate-related mumps incidence in 2013–2017 indicated that lower number of children (per primary school), rural population, population density, numbers of health institutions and inoculation rate, and higher latitude could modify the cold effect, whereas only the inoculation rate was statistically significant, with the relevant RR value: 1.82(1.00,3.31) (Fig. 7 and Table S8).

4. Discussion

This study adopted a two-stage advanced approach to explore the exposure and lag effects of meteorological factors on mumps incidence and clarified how the climate-morbidity association differed depending on gender and age, thus identify susceptible populations to climate change. Mean temperature and wind speed were found to be remarkably associated with mumps incidence. Male and adolescent aged 5–14 y were the most sensitive population to extreme weather

conditions. Several socioeconomic indicators were distinguished to modify the climate-morbidity relationship. To the best of our knowledge, this study is the first to examine the association between meteorological factors and mumps incidence at a provincial level and also the first to detect potential effect modifiers.

We found that both high and low temperatures influence the incidence of mumps in 2005–2012, which is similar to the effects of temperature variation on mortality (Li et al., 2014). Nevertheless, their effect curve is inconsistent, with temperature-related mortality characterized by V-, U-, or J-type curves. Death is more likely to be affected by extreme temperature, and the lower or higher the temperature, the greater the risk of death. In addition, a threshold of optimal temperature always exists (Guo et al., 2016; Ma et al., 2015). Similarly, the effects of low and high external temperatures on the incidence of mumps were remarkable, producing an inverted S-type curve. A temperature of 12–13 °C showed the maximum adverse effect, and no optimal temperature was found. This result may be related to the survival and replication of the mumps virus at different temperatures. The mumps virus can tolerate environmental conditions remarkably well and is relatively stable at 21 °C. The reproduction of the mumps virus decreases when the external temperature is 4 °C and rapidly declines when the external temperature is 37 °C, resulting in a remarkable loss of infectivity (Jamil et al., 2014; Sviben et al., 2016; Wright et al., 2000). This study also found that the effect of low temperature on the mumps incidence is stronger than that of high temperature. This observation may be related to the fact that Guangxi is located in the subtropical region, where the average annual temperature is relatively high. The region is less affected by the cold wave but more frequently affected by extreme high-temperature weather. Thus, people may have a certain degree of adaptability to high-temperature weather, whereas is sensitive to low temperatures. The decrease in outdoor activities and the body immunity may attribute to the cold effect. In addition, knowledge of the lag period between cold or hot effect and adverse health outcomes is crucial for public health stakeholders to develop adequate prevention plans. Consistent with most previous studies (Ma et al., 2014; Wu et al., 2013), the present study found that the hot effect was relatively short and rapid, whereas the cold effect was long and slow.

The impact of wind speed on mumps is complex. Low wind speed aggravated the incidence of mumps, whereas high wind speed may exert a certain protective effect though not obvious in this study. The result differs from that observed in Guangzhou and Jining (Li et al., 2016; Yang et al., 2014). Yang et al. suggested that wind is an important dilution and survival factor affecting the concentration of microbes. The faster the wind velocity, the less time mumps viruses remain at a single site and the more places they can reach to promote new infections (Lighthart and Mohr, 1987). However, our findings are explainable that only certain viral concentrations can produce infection. Children (0–4 years old) and adolescents (5–14 years old), who usually remain in closed classrooms, are susceptible to mumps. In the absence of wind, high concentrations of the virus can form in a localized space, thereby spreading the infection and disease. By contrast, higher wind speed corresponds to lower ambient viral concentration and fewer people infected. Hence, wind speed and respiratory diseases are negatively correlated (Cui et al., 2015; Hedlund et al., 2014). The effects of atmospheric pressure and sunshine duration on the total population were not remarkable and only were observed in adolescents. No significant relationship was found between relative humidity and mumps incidence, which was inconsistent with the results of studies performed in Guangzhou and Jining. This discrepancy may be due to the differences in climate and environment in different regions.

On the whole, subgroup analysis showed that males were more susceptible than females to extreme temperature, and wind velocity in 2005–2012. This finding may be attributed to the differences in physiology, metabolism, and environmental exposure level between males and females. Males are generally more susceptible, and females are more resistant to bacterial, viral, and parasitic infections; females have stronger innate and adaptive immune responses than males, and this difference is particularly prominent between puberty and menopause (Bouman et al., 2005; Harry Dao and Kazin, 2007; Klein and Roberts, 2015). In addition, social activities are more frequent for men than for women in China, especially in mountainous provinces, such as Guangxi. Men often have to leave their house and perform manual labor to maintain their livelihood. Therefore, they are more frequently exposed to bad weather conditions. Furthermore, male children are more physically active than female children, and they tend to play in groups, increasing the probability of exposure to viruses. The present study found that the incidence of mumps varied in different age groups. Among the different age groups, adolescents (5–14 years old) were the most sensitive to extreme meteorological conditions. This finding is attributed to the fact that adolescents (5–14 years old) spend most of their time in school, which is the main site for the spread and outbreak of infectious diseases. In this environment, the air speed is slow in the absence of wind, and physical activities rapidly decrease during cold weather and rainfall conditions (Bélanger et al., 2009), resulting in reduced immunity and local outbreaks of mumps. Students should stay warm, and classroom windows should be opened frequently to increase ventilation. Likewise, physical activities should be promoted, which may benefit the prevention and control of mumps.

In the present study, latitude, population density, GDP per capita, numbers of health institutions, highly educated population and inoculation rate exerted important modification effects on the temperature-induced incidence of mumps in 2005–2012. The difference in climatic conditions is an important source of variation in temperature-health effects between regions. A study conducted in Guangdong (China) can support this conclusion (C Guo et al., 2016). The level of GDP per capita determines whether people have the economic ability to purchase air-conditioning and other temperature-control equipment, thereby affecting the relationship between climate and human health (Xiao et al., 2017). Nevertheless, the specific mechanism of the impact of GDP on infectious diseases still need more information to clarify. Another similar study in Shandong (China) including 17 cities suggested that the number of healthcare institutions could modify the relationship between temperature and Hand-foot-mouth disease, which is consistent with the conclusion of this study, but its explanation about the source of heterogeneity is limited (Zhu et al., 2016). The allocation of adequate health resources and increased coverage of immunization can remarkably reduce the population's susceptibility to mumps and strengthen the ability to control the epidemic. Lower highly educated population can increase the risk to infections in cold environment, which may be related to the poor living condition and the weak health awareness to mumps incidence. It suggested that we should increase the propaganda of basic knowledge about infectious disease prevention and control, especially for people with low education level. In addition, the impact of population density on the mumps incidence seems unreasonable. This finding may be related to the small number of cities included in the study and the confounding effects of other unknown risk factors, which need further extensive studies for confirmation.

It is very interesting that the relationship between meteorological factors and the incidence of mumps and the modification of socioeconomic factors have all significantly weakened after 2013, which is consistent with the continued decline in the incidence of mumps and the continued weakening of seasonality during the period. The change of effect trend may be attributed to two reasons. First, the vaccine intervention is the most important influencing factor. Since April 2008, measles-mumps-rubella (MMR) was included into the national immunization program in Guangxi. Due to the limitation of the number of vaccines, it has only been implemented in some regions and inoculated for free in the total autonomous region in the following year. In 2010, the vaccination program of mumps was transferred to the Immunization Planning Institute for management. Epidemic surveillance, immunization and catch-up immunization were all strengthened. Therefore, the overall level of mumps vaccine coverage was low before

2013, and the regional difference was remarkable. The large numbers of susceptible population may facilitate the seasonal epidemics. Second, the disparities in socioeconomic and medical service capacity between different regions of Guangxi have been eased in recent years, which made the modification of socioeconomic factors less obvious. Results of analyses in 2005–2012 and 2013–2017 suggested that strengthening the coverage of vaccination and reducing the inequality of socio-economic level among regions would be crucial for the prevention and control of the mumps epidemic and effective response to extreme weather conditions.

The present study has some advantages. First, this study is based on an extensive dataset from 10 cities in Southern China over the past 13 years, making it the first to investigate the relationship between mumps and meteorological factors from two different time periods at a multi-city level, an approach that makes the results representative and stable. Second, the present study not only incorporated multiple meteorological variables but also addressed in detail how the climate–-morbidity association differed depending on gender and age, thus identifying susceptible populations to climate change. Finally, this study explored the socioeconomic factors that may affect the incidence of mumps, and several significant modifiers were distinguished. This study may serve as a reference for health agencies to formulate targeted disease prevention policies and establish early warning systems.

Despite these advantages, the present study also has some limitations. First, the mumps data used were acquired through passive monitoring; thus, the true number of infections may be underestimated. However, all cities used the same reporting standards. Hence, the level of underestimation should be similar. Meanwhile, some cases were possibly false positive as a result of relying solely on clinical symptoms for diagnosis rather than on laboratory tests. Thus, the results were not significantly affected. Second, some heterogeneity was still observed between or within regions even though 10 socioeconomic indicators were included in our study. Environmental pollution, behavioral habits, serum antibody levels in the population, and other socioeconomic factors such as air conditioning prevalence and vehicle usage rate in different regions can also become potential confounders, and further studies are needed to clarify the relationship between these factors and mumps incidence. Third, the meteorological data for each city originated from a local weather station. Although these cities are not large, the complex terrain and interlaced mountains may promote the formation of local microclimates. Therefore, the representativeness of the weather data must be considered in this study.

5. Conclusion

This study confirmed that the incidence of mumps is associated with meteorological factors (e.g., temperature, wind speed). However, the specific effects can differ depending on gender and age. Hot, cold, and windless effects can promote the incidence of mumps. Males and adolescents (5–14 years old) are more susceptible to extreme weather conditions than other subgroups. In addition, geographical latitude, population density, GDP per capita, numbers of health institutions, highly educated population and inoculation rate may have a certain degree of modification on the climate-related incidence of mumps. Human interventions may affect the pattern of climate-related incidence of mumps and reduce the population's susceptibility to extreme weather. Additional studies are needed to determine how these factors affect the risk of acquiring mumps in different populations.

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Conflict of interest

The authors declare no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2018.06.047.

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